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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/943,664	08/30/2001	Kevin P. Baker	P2548P1C8	2448

7590 03/17/2004

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EXAMINER	
O HARA, EILEEN B	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 03/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/943,664	BAKER ET AL.	
	Examiner	Art Unit	
	Eileen O'Hara	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 December 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 25-36 are pending in the instant application. Claims 22-26 have been amended and claims 22-24 have been canceled and claims 35 and 36 have been added as requested by Applicant in the Paper filed, Dec. 24, 2003.

Withdrawn Objections and Rejections

2. Any objection or rejection of record which is not expressly repeated in this action has been withdrawn.

Claim Rejections - 35 USC § 101 and § 112

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

3. Claims 25-34 remain rejected and new claims 35 and 36 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

The basis for these rejections is set forth at pp. 3-6 of previous Office Action (Paper No. 15, 24 March 2003), and pp. 5-7 of the previous Office Action , paper No. 17, and below.

Applicant's arguments (pp. 10-12, Paper filed 24 December 2003) have been fully considered but are not found to be persuasive for the following reasons.

Applicants traverse the rejection and assert that as the polypeptides encoded by an amplified DNA sequence, the polypeptides have utility as diagnostic markers for determining the

presence of tumor cells in lung and/or colon tissue samples. Applicants cite *In re Langer, In re Jolles, In re Irons and In re Sichert,* and submit that an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 USC § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility of its scope." Applicants also assert that the credibility of the asserted utility is to be assessed from the perspective of one or ordinary skill in the art in view of the disclosure and any other evidence of record. Applicants also cite *Raytheon v. Roper and In re Oetiker,* and submit that the evidentiary standard to be used throughout ex parte examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration, and thus to overcome the presumption of truth that an assertion of utility by the Applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Applicants further submit that the Examiner has not shown whether the lack of correlation observed for the family of polypeptides referenced in Pennica et al. is typical, or is merely a discrepancy, and exception to the rule of correlation.

Applicants' arguments have been fully considered but are not deemed persuasive. The Pennica et al. paper provides evidence that there is no positive correlation between DNA amplification and mRNA expression or protein expression. The paper of Haynes et al. is evidence that there is not a positive correlation between transcript abundance and protein expression. An additional reference that further supports this is the paper of Gygi et al., Molecular and Cellular Biology, March 1999, p.1720-1730, which expands the work of Haynes et al. and provides a more thorough analysis of the data. Analysis of the Haynes et al. and Gygi et al. papers shows that there is a positive correlation between only the most abundant mRNAs

and protein expressed. However, the correlation coefficient for the whole data set of the Gygi paper, 0.935, was highly biased by a small number of genes with very large protein and message levels (page 1726). Genes for which the message level was below 10 copies per cell and included 69% (73 out of 106 genes) of the data used had a correlation coefficient of only 0.356. The Gygi paper also found that levels of protein expression coded for by mRNA with comparable abundance varied by as much as 30-fold and that the mRNA levels coding for proteins with comparable expression levels varied by as much as 20-fold. As shown in Figure 6, the correlation value remained relatively stable in the range of 0.1 to 0.4 if the lowest expressed 40-95 proteins used in the study were included, but the correlation value steadily climbed by the inclusion of each of the 11 very highly expressed proteins. Therefore, the Gygi paper supports a positive correlation between mRNA expression and protein abundance only with **very highly** expressed mRNAs. The issue at hand in the instant application is whether protein is elevated and such elevation is detectable and correlative with a disease or disorder. Applicants have provided no data that would support their assertion that the amplified nucleic acid of SEQ ID NO: 49 would result in more protein, and also have supplied no references that teach that increased DNA expression results in increased protein expression. Therefore, one of ordinary skill in the art would not expect that protein from DNA amplified in a cancer would be expressed at a higher level. Absent any information about protein expression, it cannot be assumed that there is a difference in expression of the protein between normal tissue and tumors.

Applicants futher assert that even if one assumes that it is more likely than not that there is no correlation between gene amplification and increased mRNA/protein expression, a polypeptide encoded by a gene that is amplified in cancer would still have a specific and

substantially utility, and provides the declaration by Dr. Avi Ashkenazi. Dr. Ashkenazi explains that even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment, in that if the gene product is over-expressed in some tumor types but not others, this would enable more accurate tumor classification and hence better determination of suitable therapy, and additionally, if a gene is amplified by the corresponding gene product is not-overexpressed, the clinician accordingly will decide not to treat a patient with agents that target that gene product

The declaration filed under 37 CFR 1.132 filed Dec. 24, 2003 is insufficient to overcome the rejection of claims 25-34 based upon lack of utility as set forth in the last Office action because: it has not been demonstrated that the protein of the instant invention is differentially expressed in different tumors. If it was, the protein would have a specific and substantial utility for tumor classification, but the mere assertion that it may be differentially expressed does not provide a specific and substantial utility, and is an invitation to experiment. The argument that if a gene is amplified but the gene product is not over-expressed, the clinician would accordingly will decide not to treat a patient with agents that target the gene product is also insufficient to overcome the rejection of the claims. If a specific gene product was known to be involved in cancer and if there were known compounds that could be used to target the gene product, this would be an acceptable utility. However, the gene product of the instant invention has not been demonstrated to be involved in cancer. Over-expression of a gene product in a cancer cell does not necessarily mean that the gene product is involved in the cancer and that targeting the gene product would be therapeutic. Additionally, there are no known compounds that would target the gene product.

The proposed uses of the claimed invention are simply starting points for further research and investigation into potential practical uses of the claimed polypeptides. For these reasons and those of record in the previous Office Actions, the rejection under 35 USC § 101 is maintained.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4.1 Claims 25-34 also remain rejected and new claims 35 and 36 are rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. Even if the specification were enabling of how to use the PRO347 polypeptide, enablement would not be found commensurate in scope with the claims. Even if there were a patentable use for the protein of SEQ ID NO: 50, variants of 80-99% identity or conservative amino acid substitutions or amino acid additions, deletions, or substitutions, would not be enabled because the specification has not taught one of ordinary skill in the art how to use them or fragments thereof.

Applicants traverse the rejection on pages 13-14 of the response and cite MPEP§ 164.03, Assert that if one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictably in the art, and submit that the utility of the claimed polypeptide is predictable to one of skill in the art. Applicants further assert that the specification discloses at page 119, lines 27-30, that in the art, the general

presumption is that gene amplification is associated with overexpression of the gene product, and that it is predictable that a nucleic acid encoding a gene product that is amplified in tumor tissues would also encode a polypeptide that is overexpressed in tumor tissues, and such polypeptides would have utility for diagnostic markers.

Applicants' arguments have been fully considered but are not deemed persuasive. Although the specification may disclose that that gene amplification is associated with overexpression of the gene product, Applicants do not provide any references supporting this statement. As discussed above and in the previous Office Actions, the Patent Office has provided references that teach that there is no correlation between gene amplification and increased protein expression, and it is not predictable that the protein would be overexpressed.

Applicants further present the same arguments as in the traversal of the rejection under 35 USC § 101 above as regards the declaration of Dr. Ashkenazi, and which were addressed in the rejection under 35 USC § 101 above. Therefore, the rejection under 35 USC § 112 is maintained.

4.2 Claims 25-26, 33 and 34 remain rejected and new claims 35 and 36 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants traverse the rejection on pages 14-18 of the response and assert that the polypeptides of the claims are adequately described in the present application, and that Applicants have clarified that the nucleic acid is amplified in lung and/or colon tumors. Applicants cite Vas-Cath, Inc. v. Mahurkar and Amgen v. Chugai Pharmaceutical Co., and assert that in order to have possession of members of a claimed genus, the specification need not

describe all of the species that the genus encompasses, and further submit that Applicants have demonstrated possession of the claimed invention, at least by disclosure of SEQ ID NOS: 49 and 50. Applicants further assert that compliance with the written description requirement does not require an applicant to describe exactly the subject matter claimed; rather the description must clearly allow a person of ordinary skill in the art to recognize that he or she invented what is clamed, and such analysis may be performed by numerous methods several of which are described in the Guidelines, and submit that the present situation is analogous to Example 14 on pages 53-55 of the Written Description Training Materials, as the claimed polypeptides must have at least 95% identity to SEQ ID NO: 50, and possess the specified biological function, that of being encoded by a nucleic acid that is amplified in lung and/or colon tumors.

Applicants' arguments have been fully considered but are not deemed persuasive. Under the Guidelines for Examination of Patent Applications under 35 U.S.C. § 112, first paragraph, "Written Description", a representative species may be adequately described through its structure, through its functional characteristics, or through a combination of its structure and function. The specification has disclosed a single polypeptide, and there is no recited biological function for the protein. The limitation of being encoded by a nucleic acid that is amplified in lung or colon tumors is not a biological activity of the protein. Therefore, the rejection is maintained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. Claims 22-34 remain rejected and new claims 35 and 36 are rejected under 35 U.S.C. 102(a) as being anticipated by Botstein et al., WO 99/35170, July 15, 1999, claims 22-27, 31, 33 and 34 remain rejected under 35 U.S.C. 102(a) as being anticipated by Holtzman, WO 99/54343, Oct. 28, 1999, and claims 22-27, 31, 33 and 34 remain rejected under 35 U.S.C. 102(e) as being anticipated by Holtzman et al., US Patent Application Publication US20020028508, effective filing date, April 23, 1998.

Applicants traverse the rejections and assert that they have demonstrated that the proper priority date of the instant application is Dec. 22, 1998, before the Botstein et al. and Hotlzman were published or filed, and therefore the grounds of rejection have been overcome.

Applicants' arguments have been fully considered but are not deemed persuasive, because Applicants have not overcome the utility rejection. Therefore, the rejections are maintained.

It is believed that all pertinent arguments have been answered.

New Rejections
Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 33-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6.1 Claims 33 and 34 are indefinite because they depend upon cancelled claim 22.

6.2 Claim 35 is also indefinite because it encompasses a polypeptide comprising the sequence of SEQ ID NO: 50 with conservative amino acid substitutions. This is considered indefinite, since there is no limit on the number of conservative amino acid substitutions that may be made, and the resulting claim does not clearly set forth the metes and bounds of the patent protection desired.

Conclusion

7. No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (571) 272-0878. The examiner can normally be reached on Monday through Friday from 10:00 AM to 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached at (571) 272-0871.

Official papers Before Final and After Final filed by RightFax should be directed to (703) 872-9306.

The customer service RightFax number is (703) 872-9305.

Official papers filed by fax should be directed to (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Eileen B. O'Hara, Ph.D.

Patent Examiner

Lorraine Spector

LORRAINE SPECTOR
PRIMARY EXAMINER